

Renal and circulatory dysfunction in cirrhosis: Current management and future perspectives

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Chronic liver diseases are amongst the top leading causes of death in Europe as well as in other areas of the world [1–3]. Chronic liver diseases are characterized by unrelenting progression of liver inflammation and fibrosis over a prolonged period of time, usually more than 20 years, which may eventually lead to cirrhosis [4]. Advanced cirrhosis leads to a complex syndrome of chronic liver failure which involves many different organs besides the liver, including the brain, heart and systemic circulation, adrenal glands, lungs, and kidneys [5]. The high morbidity and mortality secondary to chronic liver failure is due to complications related to the dysfunction of these organs, either alone or, more frequently, in combination. Understanding the mechanisms leading to organ dysfunction is crucial to the development of strategies for treatment and prevention of complications of cirrhosis. This article reviews our current knowledge, as well as future perspectives, on the management of circulatory and renal dysfunction in chronic liver failure.

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A brief review of the current understanding of renal and circulatory dysfunction in cirrhosis

A wealth of evidence indicates that impairment in circulatory function is the main cause of renal dysfunction in cirrhosis. The dysfunction in the systemic arterial circulation is largely characterized by a reduction in systemic vascular resistance due to primary arterial vasodilation of the splanchnic circulation triggered by portal hypertension [6–9]. The relationship between liver disease, portal hypertension, and abnormalities in splanchnic circulation is discussed in detail in several recent reviews [4,10,11]. The vasodilation of the splanchnic arterial circulation is due to an increased production/activity of vasodilator factors, particularly nitric oxide, carbon monoxide, and endogenous cannabinoids [7–13].

At the early stages of cirrhosis, when patients are usually asymptomatic and with normal physical status, the increase in hepatic vascular resistance, mainly due to fibrosis, is moderate and therefore the increase in portal pressure is also moderate. In this context, there is a slight reduction in systemic vascular resis-

tance due to moderate splanchnic arterial vasodilation which is compensated by an increase in cardiac output, thus permitting arterial pressure and effective arterial blood volume to remain within normal limits [6,7]. In advanced stages of cirrhosis, when patients are usually symptomatic and have already developed some complications of the disease, the reduction in systemic vascular resistance is marked and cannot be compensated by further increases in cardiac output; therefore, underfilling of the arterial circulation develops, there being a disarrangement between the intravascular blood volume and a very enlarged intravascular arterial circulation [7]. Moreover, evidence indicates that at this stage of the disease there is a reduction in the cardiac output that contributes to the arterial underfilling [14]. In this context of marked underfilling of the arterial circulation, arterial pressure must be maintained by the activation of vasoconstrictor systems, including the renin–angiotensin–system, the sympathetic nervous system, and, at late stages, a non-osmotic hypersecretion of arginine vasopressin (the antidiuretic hormone) [7]. These systems help maintain effective arterial blood volume and arterial pressure but have important effects on kidney function, particularly sodium and solute-free water retention with accumulation of ascites and edema. If the activation of these systems is extreme, renal vasoconstriction leading to markedly reduced glomerular filtration rate may occur, a condition known as hepatorenal syndrome (HRS) [7,8]. Other factors that may contribute to the development of HRS are vasoactive mediators acting on the intrarenal circulation. An increased synthesis of several vasoactive factors in the intrarenal circulation, which may affect renal blood flow or glomerular filtration rate, such as cysteinyl leukotrienes, thromboxane A₂, F₂-isoprostanes, and endothelin-1, has been reported, yet the role of these factors in the pathogenesis of HRS remains poorly understood [6]. Nonetheless, a role for endothelin-1 is unlikely since the administration of the endothelin antagonist tazosentan does not improve renal function in patients with type 2 HRS [15]. Recent data indicate that impairment in the cardiac function, likely due to cirrhotic cardiomyopathy, is a risk factor for the development of HRS and likely further contributes to the impairment of the arterial blood volume that is related to splanchnic vasodilation [16,17]. A summary of the pathogenesis of ascites and functional renal abnormalities with possible therapeutic interventions are shown in Figs. 1–3.

A wealth of evidence indicates that altered splanchnic hemodynamics is related to the development of portal hypertension [11]. On the other hand, studies in both experimental animals and patients with cirrhosis suggest that bacterial translocation, the

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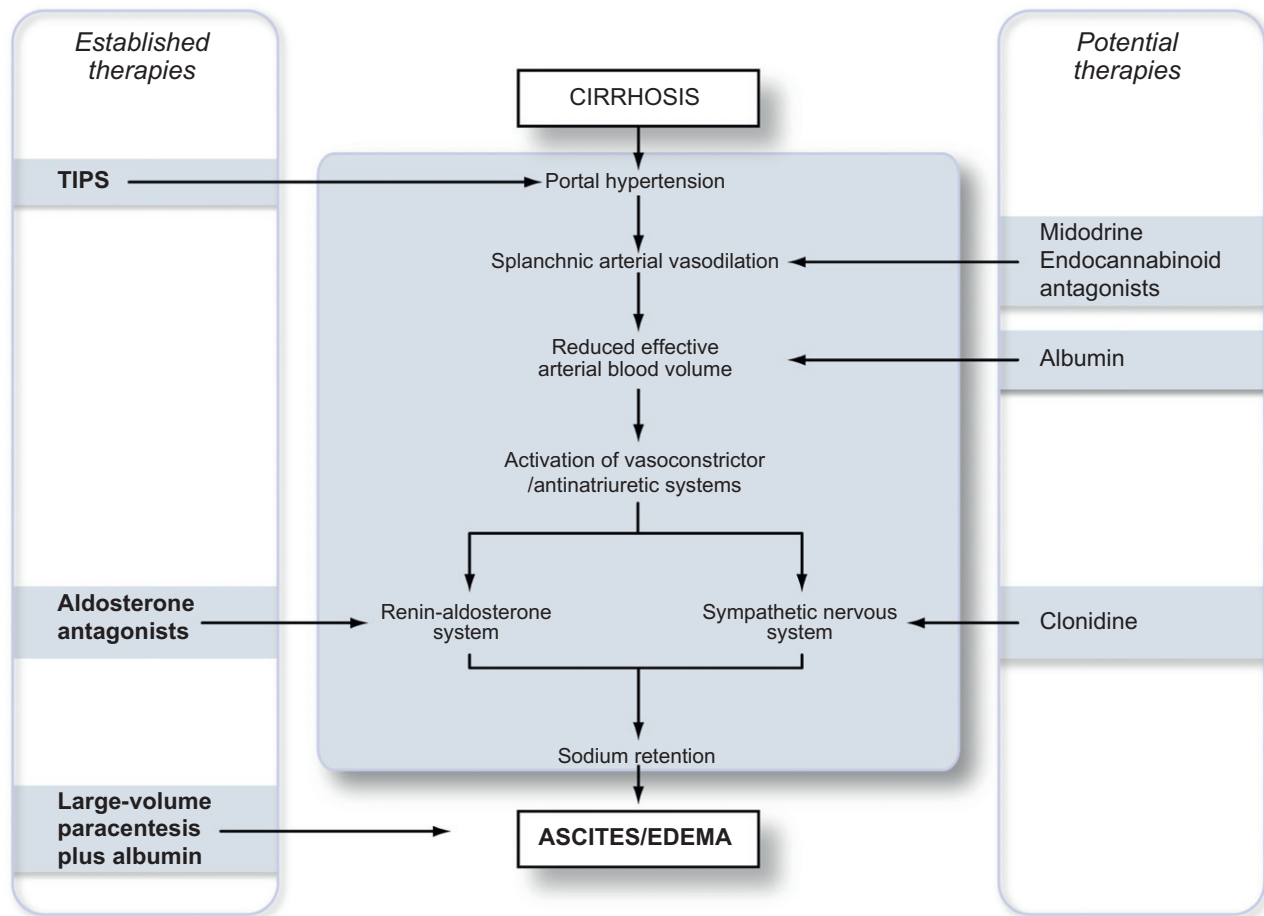


Fig. 1. Schematic representation of the proposed pathogenesis of ascites and edema formation in cirrhosis. Established therapies are given on the left side and potential new therapies on the right. TIPS, transjugular intrahepatic portosystemic shunt.

passage of bacteria from the intestinal lumen to mesenteric lymph nodes, may play an important role in circulatory dysfunction in advanced cirrhosis [18,19]. Bacterial translocation may elicit an inflammatory response with increased production of proinflammatory cytokines in the splanchnic area, which may in turn lead to vasodilatation of the splanchnic arterial vessels. Patients with cirrhosis and increased levels of lipopolysaccharide-binding protein or circulating levels of bacterial DNA, which are considered surrogate markers of bacterial translocation, have higher serum levels of cytokines, lower systemic vascular resistance, and higher cardiac output when compared to those who do not [20,21]. The important role of bacterial translocation in circulatory dysfunction is further supported by the observation that the administration of norfloxacin, an antibiotic that causes selective intestinal decontamination, improves circulatory function [22,23].

The expanded extracellular fluid volume: ascites and edema

Sodium is the main determinant of the volume of the extracellular fluid (ECF). In healthy subjects the amount of sodium is maintained constant through a very precise equilibrium between sodium intake and sodium excretion by the kidneys [24,25]. In advanced cirrhosis, this equilibrium is lost because of an increased retention of sodium in the kidneys and positive sodium

balance develops leading to expansion of the ECF [26,27]. The excess of ECF is mainly stored in the peritoneal cavity (because of the high pressure of the splanchnic capillaries due to portal hypertension) and in the interstitial tissue of the legs (because of the high pressure of the capillaries of the lower extremities), causing ascites and edema, respectively. Excessive ECF may also be stored in other locations, such as the pleural space, causing pleural effusion. Ascites and edema are the most frequent complication of patients with advanced chronic liver diseases.

Current management

The current management of ascites and edema is based on dietary salt restriction together with diuretics to increase renal sodium excretion [28] (Table 1). The aim of the treatment is therefore to achieve a natriuresis higher than sodium intake that causes negative sodium and fluid balance with weight loss and reduction in the ECF volume. The diuretics of choice are aldosterone antagonists, because of the increased aldosterone secretion present in cirrhosis [29]. Administration of loop diuretics (mainly furosemide) in combination with aldosterone antagonists may be helpful in patients with recurrent ascites [28]. Diuretic treatment is effective in more than two thirds of patients with ascites. Doses of diuretics should be adjusted according to several factors, particularly whether the episode of ascites is the first or recurrent,

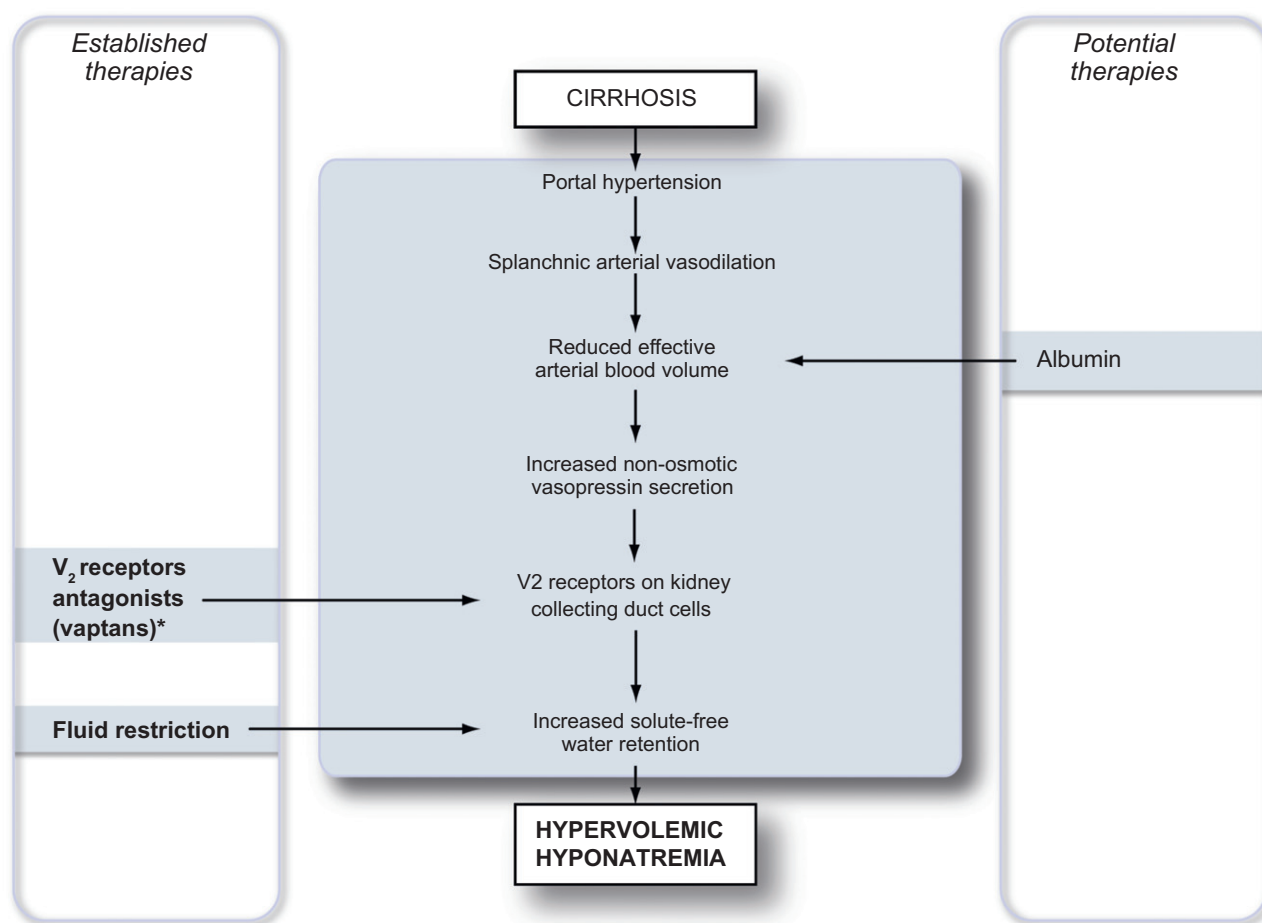


Fig. 2. Schematic representation of the proposed pathogenesis of hypervolemic hyponatremia in cirrhosis. Established therapies are given on the left side and potential new therapies on the right. *Vaptans are approved for the management of hypervolemic hyponatremia in cirrhosis in United States and Japan, but not in Europe.

severity of sodium retention, presence of renal impairment, and electrolyte abnormalities. The management of ascites and edema with diuretics is not simple and requires a great deal of experience to achieve a high efficacy and at the same time minimizing the risk of diuretic-induced complications. Several guidelines for diuretic use have been reported recently [28,30–32]. There are two main drawbacks of diuretic therapy for ascites: the lack of efficacy in approximately 10–20% of patients and the development of complications, particularly hepatic encephalopathy, renal impairment, and electrolyte disturbances, which have been reported in up to 40% of patients. Therefore, there is a clear need for improving our current therapy of ascites.

Key points 1. Management of ascites

- The management of moderate ascites is based on sodium restriction plus aldosterone antagonists.
- Loop diuretics are helpful in combination with aldosterone antagonists in patients with recurrent ascites.
- Large-volume paracentesis plus albumin is the treatment of choice for large ascites.
- The first-line treatment for refractory ascites is repeated large-volume paracentesis plus albumin.
- TIPS is a second-line treatment for refractory ascites.

The problems with diuretic therapy gave rise to another approach for management of ascites which is large-volume paracentesis (LVP, i.e. removal of large amounts of ascitic fluid) [33]. LVP is very effective and is the treatment of choice for both patients with large ascites and those with recurrent ascites due to lack of response to diuretics (i.e. refractory ascites) [28,30–32]. LVP requires the associated administration of albumin to prevent an impairment of circulatory function that may occur with the removal of large amounts of ascitic fluid [34]. The main disadvantages of LVP are that it is time consuming, involves the administration of albumin, which is not easily available in all settings, and does not prevent the recurrence of ascites because it does not interfere with the main mechanisms of ascites formation. An alternative approach to treatment with LVP and albumin for patients with an unresponsive ascites (refractory ascites) is the use of transjugular intrahepatic portosystemic shunts (TIPS). TIPS consist of an autoexpandable stent inserted through a transjugular approach which causes a remarkable reduction in portal pressure and decreases renal sodium retention. Although effective in the management of ascites, the use of TIPS has significant disadvantages over LVP plus albumin, including its limited applicability (it cannot be used in patients with severe liver failure or recurrent hepatic encephalopathy), high cost, increased risk of hepatic encephalopathy, and need of expertise for its insertion [35–38]. On this basis, TIPS is con-

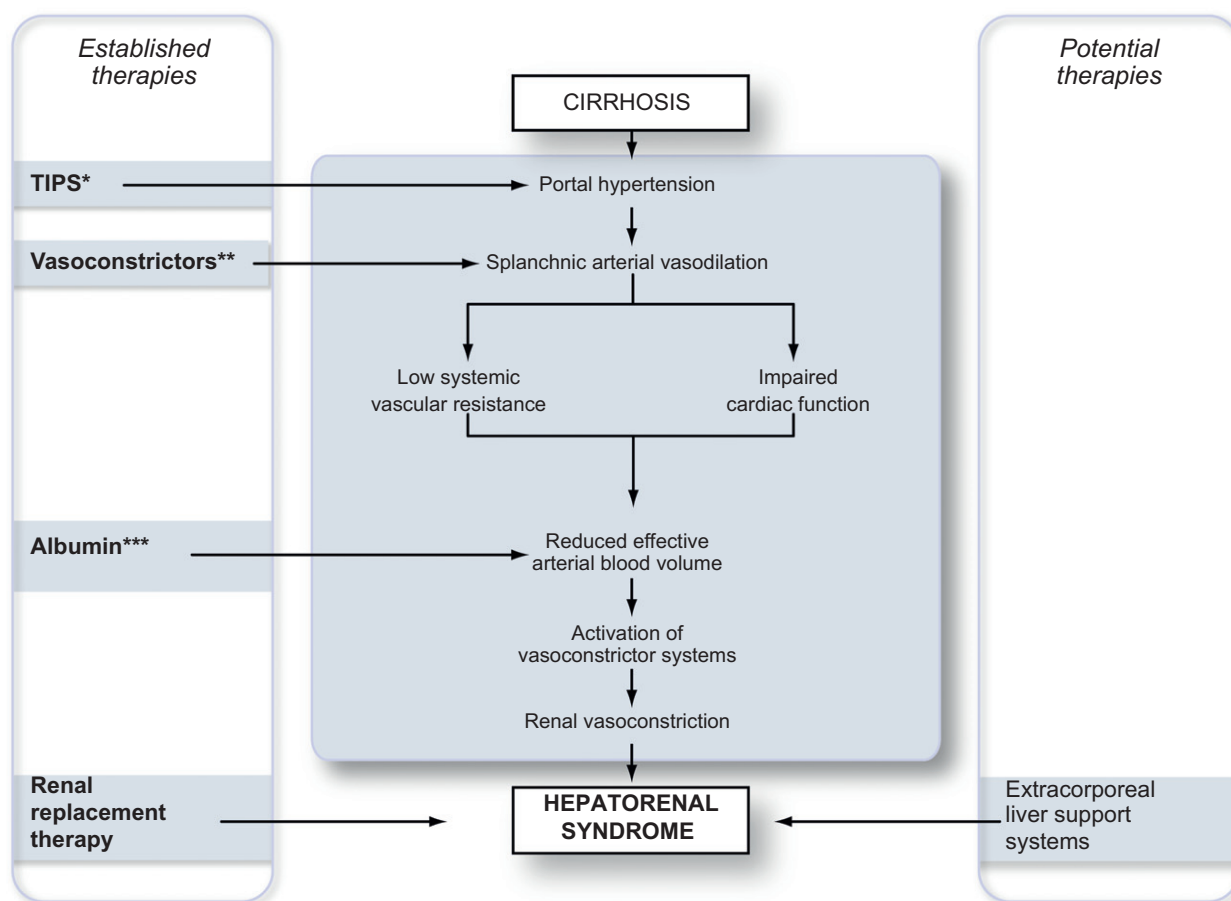


Fig. 3. Schematic representation of the proposed pathogenesis of hepatorenal syndrome in cirrhosis. Established therapies are given on the left side and potential new therapies on the right. *The use of TIPS, transjugular intrahepatic portosystemic shunt, has been reported in some studies but the information is very limited. **Vasoconstrictors include vasopressin analogues such as terlipressin and α -adrenergic agonists, such as norepinephrine or midodrine. ***Albumin is given in combination with vasoconstrictors. Albumin alone is seldom effective.

sidered a second-line therapy for refractory ascites in all recent guidelines [28,30–32].

Besides their efficacy in preventing variceal bleeding, non-selective β -blockers could have beneficial effects on the prevention of other complications of cirrhosis by reducing portal pressure, including development of ascites. Patients demonstrating a positive response to β -blockers, that is characterized by marked reduction in hepatic venous pressure gradient, afterwards show a decreased risk of ascites development during follow-up compared to patients who display no response [39,40]. In apparent contradiction with these findings, a recent study showed that in patients with refractory ascites, treatment with β -blockers was an independent risk factor for mortality, suggesting that these drugs may have deleterious effects in patients with advanced cirrhosis [41]. The results of this study indicate that the issue of benefit vs. risk of treatment with β -blockers in patients with cirrhosis deserves an extensive investigation.

Future therapeutic options

The ideal therapeutic approach to management of ascites and edema in cirrhosis would consist of a drug able to reverse the circulatory dysfunction present in cirrhosis (which would suppress

the mechanisms responsible for sodium retention) with or without combination with diuretics to enhance the excretion of the sodium retained together with the fluid. Although this ideal drug does not exist at present, several methods to improve the management of ascites have been attempted or are currently under investigation (Table 1).

Two different approaches have been investigated using drugs that interact with the activity of the sympathetic nervous system. In the first approach, the administration of clonidine, a drug that causes a suppression of the sympathetic nervous outflow from the central nervous system, in patients with cirrhosis and ascites was associated with lower ascites recurrence and reduced need for diuretic administration compared to a control group of patients receiving standard therapy without clonidine [42]. The beneficial effects of this approach are probably related to suppression of the afferent sympathetic activity to the renal nerves which has been shown to participate in renal sodium retention [43,44]. In a second approach, that appears contradictory with the previous one, the administration of midodrine, an orally active α -adrenergic agonist, in patients with cirrhosis and ascites improved circulatory function, as indicated by an increase in arterial pressure and suppression of the activity of the renin-angiotensin and sympathetic nervous systems [45,46]. This

Table 1. Treatment of ascites: current management and potential future options.

Current management	Potential future options
First line therapy:	Sympathetic nervous system inhibition: clonidine α -adrenergic agonists: midodrine
Dietary salt restriction	Albumin administration
Combined diuretic treatment	Albumin combined with midodrine
Aldosterone antagonists	Endocannabinoid antagonists
Loop diuretics	
Large volume paracentesis and albumin	
Second line therapy:	
TIPS *	

*TIPS, transjugular intrahepatic portosystemic shunt.

improvement in circulatory function was associated with increases in renal plasma flow, glomerular filtration rate, and urinary sodium excretion. However, in these studies, midodrine was given for a short period of time and its potentially beneficial effects in the management of ascites and edema have not yet been assessed. No significant side effects were reported in these two short-term studies, but the long-term safety is unknown. It would be worthwhile to perform studies in a large series of patients to assess the usefulness of both approaches in the long-term management of ascites.

The administration of albumin has potentially beneficial effects on circulatory function in patients with cirrhosis [47]. Moreover, a prospective study in patients with cirrhosis and ascites showed that the long-term administration of albumin increased survival compared to a control group of patients not receiving albumin [48]. Nevertheless, the usefulness of this approach requires validation in other studies before it becomes a standard of treatment for patients with cirrhosis. An interesting approach to improve circulatory and renal function in cirrhosis is to combine the administration of albumin together with clonidine or midodrine. This approach is currently being tested in patients in the waiting list for liver transplantation (www.clinicaltrials.gov).

In contrast to these approaches that show promising results, there have been a number of other approaches that have failed in recent years. An increased production of the vasodilator factor nitric oxide likely plays a major role in the development and maintenance of splanchnic arterial vasodilation in cirrhosis [9,49]. Moreover, in experimental cirrhosis the normalization of the overproduction of nitric oxide is associated with an improvement of renal and circulatory function and reduction/disappearance of ascites [50]. Unfortunately, the inhibitors of the nitric oxide system were withdrawn from development because of important side effects in patients with septic shock [51].

In contrast to the splanchnic and systemic circulation in which there is overproduction of nitric oxide, in the intrahepatic circulation the production of nitric oxide is markedly decreased, which may be a factor contributing to an increased intrahepatic vascular resistance and portal hypertension [10,52]. Therefore, the hypothesis was raised that increasing NO in the intrahepatic circulation could have beneficial effects in portal pressure. Attempts to decrease portal hypertension by the selective deliv-

ery of nitric oxide to the liver were promising in experimental portal hypertension but have so far failed in human cirrhosis [53,54].

Recent studies in experimental animals with cirrhosis suggest that the endocannabinoid system plays a role in the splanchnic vasodilation of cirrhosis and that inhibition of the endocannabinoid system with the use of CB1 endocannabinoid antagonists improves renal function and sodium excretion in experimental cirrhosis [55–57]. Unfortunately, rimonabant, a drug that antagonizes both central and peripheral CB1 receptors, was recently withdrawn from the market in Europe (the drug was not approved in the USA) due to an increased risk of depression in patients treated for obesity. This approach to management of ascites will have to be re-explored if selective antagonists of the peripheral CB1 receptors become available.

A final approach that has been tested in recent years is whether the combination of diuretics with satavaptan, a drug that selectively antagonizes the renal V2 receptors of vasopressin, the antidiuretic hormone, could improve the management of ascites [58]. In phase 2 studies, the combination of satavaptan with diuretics for a short period of time was associated with a decrease in ascites volume and reduced the need for large-volume paracentesis in patients with difficult-to-treat ascites [59–61]. Nevertheless, phase 3 double-blind studies showed that when this combination was used for prolonged periods of time, the effectiveness in the control of ascites was very limited and treatment was associated with an increased mortality compared to a control group of patients receiving placebo plus standard therapy with diuretics alone [62,63]. The reason for this increased risk of death in patients receiving satavaptan in combination with diuretics for the long-term treatment of ascites is currently unknown.

The disturbed renal water homeostasis: hypervolemic hyponatremia

Hypervolemic hyponatremia is a frequent complication of patients with advanced cirrhosis that consists of a decreased serum sodium concentration in the setting of an expanded extracellular fluid volume with ascites and edema [64]. It is generally accepted that the main pathogenic factor of hypervolemic hyponatremia is an

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impairment of renal solute-free water excretion secondary to an excessive production of vasopressin stimulated by circulatory dysfunction, yet other factors may also participate [64]. Some patients develop hypervolemic hyponatremia in the setting of a preserved renal capacity to eliminate solute-free water [65]. The pathogenesis of this latter disorder is unknown and deserves investigation. The interest in hypervolemic hyponatremia has been fostered by the observation that hyponatremia is a risk factor of hepatic encephalopathy and death [66–71].

Hypervolemic hyponatremia should be differentiated from hypovolemic hyponatremia, a less common condition characterized by low sodium levels in the setting of contraction of the extracellular fluid volume and plasma volume due to marked and prolonged loss of sodium. This condition is managed by withdrawing the cause of sodium loss (usually diuretics) and administration of saline solutions and will not be discussed further in this review.

Current management

For many years there has been no effective pharmacological therapy for the management of hypervolemic hyponatremia. Several drugs, including demeclocycline and κ -opioid agonists, were found to increase serum sodium concentration in pilot studies, but were abandoned due to side effects [72,73]. Because of the absence of effective drugs, treatment has relied on fluid restriction (to approximately 1 L/day) with the aim of causing a negative fluid balance. However, since urine volume is low in these patients, a negative fluid balance is infrequently achieved. This is the reason why fluid restriction is seldom effective in increasing serum sodium concentration in these patients. Hypertonic saline has been used but it is usually not effective and markedly increases ascites and edema due to the intense sodium retention present in these patients. Therefore, its use is not currently recommended [28].

In recent years, a new generation of drugs, known as vaptans, which selectively antagonize the vasopressin V2 receptors present in the renal tubules, has come into play [58]. Some of these drugs are currently licensed for hyponatremia associated with high vasopressin levels. In the US, conivaptan (a dual V1/V2 antagonist) was approved few years ago for short-term (5 days) intravenous use. More recently, tolvaptan (a selective oral V2 antagonist) was approved by the FDA for severe hyponatremia (<125 mmol/L) associated with cirrhosis, cardiac failure, and the syndrome of inappropriate antidiuretic hormone secretion (SIADH). In Europe, conivaptan is not available and tolvaptan is approved only for SIADH. There is very little information on conivaptan use in patients with cirrhosis [74]. In randomized studies, the administration of tolvaptan to patients with cirrhosis and hypervolemic hyponatremia induced a marked increase in urine volume and solute-free water excretion and a significant increase (normalization in some patients) in serum sodium levels [75,76]. Reversal of hyponatremia was associated with an improvement of the mental component of a quality of life score, suggesting a beneficial effect of the enhanced serum sodium levels on cerebral function. No adverse effects were noticed in these studies, except for thirst and a remarkable increase in urine volume in some patients. Unfortunately, however, the duration of tolvaptan therapy in these studies was of only one month. The Clinical Practice Guidelines of the European Association for the Study of the Liver (EASL) recommend tolvaptan for short-term management of

patients with severe hypervolemic hyponatremia (<125 mmol/L) [28]. Treatment should be initiated in the hospital at low doses (15 mg/day) with frequent monitoring of serum sodium to avoid a rapid increase in serum sodium concentration (<8 – 10 mmol/day) and the dose increased stepwise until a normalization of serum sodium levels has been achieved. Neither fluid restriction nor hypertonic saline should be used concomitantly with tolvaptan to avoid a too rapid increase in serum sodium concentration. Treatment may be particularly useful in patients with hyponatremia who have to undergo surgery, particularly liver transplantation, to reduce the increased risk of complications after transplantation in patients with hyponatremia [77]. It is likely that the improvement/normalization of serum sodium concentration may reduce the risk of severe neurological complications in these patients, particularly central pontine myelinolysis. Nonetheless, more information is needed on the use of vaptans in the management of hypervolemic hyponatremia in cirrhosis, particularly with respect to its long-term safety. This is important because, as mentioned before, the development of one of these drugs, satavaptan, was stopped because of the finding of increased frequency of complications and reduced survival compared to placebo in a phase 3 study assessing the efficacy of this drug in the management of ascites in patients with cirrhosis [63].

Future therapeutic options

The future of management of hypervolemic hyponatremia in cirrhosis is likely linked to the use of vaptans. However, there are several aspects of the use of vaptans that are worth of comment. First, the cautious use of vaptans cannot be overemphasized. Treatment should be started in the hospital and patients monitored closely during the treatment, and serum sodium levels measured at regular intervals, particularly at the beginning of the treatment, when the dose is increased or whenever there is a change in the clinical status of patients. Second, there is increasing evidence that patients with hyponatremia represent a heterogeneous population; therefore, it is of major importance to understand which patients are to benefit from treatment with vaptans. Finally, there is a need for data on long-term safety and efficacy of treatment with vaptans in patients with cirrhosis and hypervolemic hyponatremia. Another approach, besides vaptans, that would be of interest for the future, is the administration of albumin since some studies have shown that repeated albumin administration improves serum sodium concentration in patients with cirrhosis and severe hyponatremia [78,79].

The fascinating concept of functional renal vasoconstriction: hepatorenal syndrome

Hepatorenal syndrome (HRS) is a unique form of renal failure that develops in patients with cirrhosis, in the absence of significant histological abnormalities in the kidneys [80]. Until recent years, the only therapeutic method capable of reversing HRS was liver transplantation. Currently, reversal of HRS is achieved with treatment with vasoconstrictor drugs associated with albumin [81–83]. As mentioned before, it is generally accepted that HRS is of circulatory origin and occurs as a consequence of reduction in renal blood flow and glomerular filtration rate secondary to marked arterial vasodilation in the splanchnic circulation. This leads to a reduction in effective arterial blood volume and arterial

pressure with compensatory activation of vasoconstrictor systems, particularly sympathetic nervous system and renin–angiotensin–aldosterone system. An extended discussion of the pathophysiology of HRS can be found elsewhere [81,84,85]. HRS characteristically develops after a precipitating factor, particularly a bacterial infection, most frequently spontaneous bacterial peritonitis, although in some cases it may develop without an identifiable precipitating factor. HRS occurs in two different forms: type-1 HRS, characterized by rapidly progressive renal failure usually in the setting of multiorgan failure, and type 2 HRS characterized by less severe and stable renal failure, which is clinically apparent by ascites refractory to diuretic therapy. The former is associated with a 1 month mortality rate greater than 50%, whereas the latter shows a better survival [86].

Current management

The most effective method currently available for the management of HRS is the administration of vasoconstrictor drugs (Table 2). The vasoconstrictor of choice is the vasopressin analogue terlipressin [28]. The rationale for the use of terlipressin in HRS is to improve the markedly impaired circulatory function by causing vasoconstriction of the extremely dilated splanchnic vascular bed, increasing arterial pressure, and suppressing the activity of the endogenous vasoconstrictor factors acting on the kidney [87,88]. Terlipressin is effective in 40% to 50% of patients with type-1 HRS [81,82,87]. Treatment is usually started at a dose of 1 mg/4–6 h (iv bolus) and increased to a maximum of 2 mg/4–6 h if there is no reduction in serum creatinine of at least 25% compared to the baseline value at day 3 of therapy. Responder patients usually show a progressive reduction in serum creatinine over several days and up to 1–2 weeks, together with an increase in arterial pressure, urine volume, and serum sodium concentration. Treatment is maintained until serum creatinine decreases to 1–1.2 mg/dl (88–106 μ mol/L). Predictive factors of response are, pretreatment serum bilirubin levels lower than 10 mg/dl and an increase in mean arterial pressure greater than 5 mm Hg after 3 days of treatment [89]. Recurrence of HRS after withdrawal of therapy occurs in less than 15% of patients and retreatment with terlipressin is generally effective. The most fre-

quent side effects of treatment are cardiovascular or ischemic complications, which have been reported in 12% of patients, yet most studies excluded patients with known severe cardiovascular or ischemic conditions [81,87]. Terlipressin is given in combination with albumin (1 g/kg on day 1 followed by 40 g/day) to improve the effect of treatment on circulatory function [90]. Whether terlipressin improves survival in patients with HRS is not known, but a recent systematic review of randomized studies using terlipressin as well as other vasoconstrictors showed an increased short-term survival compared with control patients [82]. The effectiveness of terlipressin in the treatment of HRS with active bacterial infection is unknown, because all clinical trials have excluded patients with ongoing infections. Finally, treatment with terlipressin in patients with type 2 HRS is also associated with an improvement of renal function [91,92]. Nevertheless, there is still limited information on the use of terlipressin in type 2 HRS.

Vasoconstrictors other than terlipressin that have been used in the management of type-1 HRS include noradrenaline and midodrine (plus octreotide), both in combination with albumin. Midodrine is given orally at doses starting from 2.5 to 75 mg/8 h and octreotide 100 μ g/8 h subcutaneously, with an increase to 12.5 mg/8 h and 200 μ g/8 h, respectively, if there is no improvement in renal function [93,94]. Noradrenaline (0.5–3 mg/h) is administered as a continuous infusion and the dose increased to achieve a raise in arterial pressure [95]. Although both vasoconstrictor drugs improve renal function, the number of patients reported so far using these treatments is very small and no randomized comparative studies have been performed to evaluate its efficacy compared with placebo.

Key points 2. Management of type-1 hepatorenal syndrome

- Patients with type-1 HRS should be considered for liver transplantation.
- The management of type-1 HRS is based on administration of vasoconstrictors plus albumin.
- Terlipressin is the vasoconstrictor of choice for the management of type-1 HRS.
- Type-1 HRS should be treated before liver transplantation.
- There is insufficient data to use TIPS as well as extracorporeal liver support systems in patients with type-1 HRS.

Table 2. Treatment of hepatorenal syndrome: current management and potential future options.

Current management	Potential future options
First line therapy :	Terlipressin used as continuous infusion
Liver transplantation	Terlipressin followed by TIPS
Terlipressin with albumin	Extracorporeal liver support systems
Second line therapy:	
Other vasoconstrictor drugs with albumin:	
Noradrenaline	
Midodrine	
TIPS*	
Renal replacement therapy	

*TIPS, transjugular intrahepatic portosystemic shunt.

Although TIPS may reverse HRS in some patients, the applicability of TIPS in patients with type-1 HRS is low because TIPS is contraindicated in patients with severe liver failure and hepatic encephalopathy, which are common findings in the setting of type-1 HRS [96]. Due to the paucity of data, more studies are needed for assessing the use of TIPS in patients with HRS. Renal replacement therapy (RRT) has been used in the management of patients with type-1 HRS, especially in patient candidates for liver transplantation, in an attempt to maintain patients alive until liver transplantation is performed [97,98]. Although RRT is not the first line therapy, it is a temporary option in patients not responding to vasoconstrictors or in those who develop severe volume overload, metabolic acidosis and/or refractory hyperkalemia. Most patients develop important side effects during hemodialysis including severe arterial hypotension, bleeding, and infections that may contribute to death during treatment.

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All patients with HRS should be considered for liver transplantation, unless they have contraindications [99]. The main problems of liver transplantation for HRS are the high waiting list mortality rate and an increased morbidity and mortality after transplantation. Nevertheless, the survival of patients with HRS treated with liver transplantation is approximately 60% at 3 years, a survival rate much higher than that expected by the natural course of the disease.

There have been few studies on the prevention of HRS. The administration of albumin (1.5 g/kg at diagnosis and 1 g/kg at day 3) is effective in the prevention of HRS secondary to SBP and has been shown to improve survival [100]. Short-term treatment (4-week) with pentoxifylline (400 mg three times a day) was shown to prevent the development of HRS in patients with severe alcoholic hepatitis [101]. In a more recent study, long-term treatment with pentoxifylline was associated with reduced frequency of some complications of cirrhosis, including renal failure, yet this was not the primary end-point of the study [102]. More studies are needed to assess the usefulness of pentoxifylline in the prevention of HRS. Finally, long-term administration of norfloxacin to patients with advanced cirrhosis (severe liver failure with or without renal impairment or hyponatremia) (400 mg/day) reduced the incidence of HRS and improved survival compared with placebo [103]. The potential mechanism(s) by which pentoxifylline and norfloxacin prevent HRS in cirrhosis is/are not well understood, but may be related, at least in part, to a reduction in cytokine levels that may have deleterious effects on renal function.

Future therapeutic options

Approximately 50–60% of patients with HRS do not respond to treatment with vasoconstrictors [89]. Therefore, one of the main challenges for the future is to increase the number of patients with HRS responding to pharmacological therapy. The first step in improving the efficacy of pharmacological therapy is to understand the pathogenic reasons for the lack of response. In this regard, it would be important to perform studies in a large series of patients with the aim of identifying predictive factors of response. Possible approaches to improve the efficacy of vasoconstrictors include modifications in the method of administration of the drugs and the combination of vasoconstrictors with other therapies (Table 2). Preliminary results of an ongoing study suggest that terlipressin is more effective when given as continuous infusion than as iv bolus [104]. This might be to a lesser effect related to the drug in impairing cardiac function in the former compared to the latter method of administration [105]. A single study in a very small series of patients suggests that treatment with vasoconstrictors, followed by insertion of TIPS, is associated with a marked improvement of renal function and prolonged survival [94]. This combined approach would require confirmation in a larger series of patients. An increased renal adenosine production has been suggested to play a role in the pathogenesis of HRS [106]. On this ground, the potential benefit of antagonizing the effects of adenosine on renal function was investigated. Unfortunately, the administration of an antagonist of A1 adenosine receptors, increased natriuresis but did not improve glomerular filtration rate and no further studies have been published investigating the use of adenosine receptors since 1998 [107]. Considering the potential relationship between impairment of cardiac function and occurrence of HRS mentioned earlier in this article [16], the possibility of treating HRS by improving cardiac

function should be investigated. Finally, two recent studies suggest that the so called extracorporeal liver support systems (either albumin dialysis using the molecular adsorbent recirculating system -MARS[®]- and fractionated plasma separation and adsorption -Prometheus[®]-) may be effective in the management of HRS [108–110]. The beneficial effects of such a therapy may be related to the improvement in circulatory function related to the elimination of vasodilator substances [111–113]. Studies specifically designed to address the efficacy and safety of extracorporeal liver support systems in patients with HRS should be performed to answer definitively the question of the potential effectiveness of such therapies in HRS.

Conflict of interests

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